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Dr. Juan S. Bonifacino received his Ph. D. degree in Biochemistry from the University of Buenos Aires, Argentina, in 1981. He then moved to the National Institutes of Health, in Bethesda, Maryland, to pursue post-doctoral studies with Dr. Richard D. Klausner. He rose through the ranks and in 1997 he became the Chief of the Cell Biology and Metabolism Branch (CBMB), now Cell Biology and Metabolism Program (CBMP), NICHD, NIH. In 2008, he was appointed NIH Distinguished Investigator. Throughout his career, Dr. Bonifacino has been interested in the molecular mechanisms that determine protein localization and fate in the secretory and endocytic pathways. Since the early 1990s, Dr. Bonifacino's group at the NIH has conducted research on signals and adaptor proteins that mediate protein sorting to endosomes, lysosomes and related organelles. His group discovered new sorting signals and adaptor proteins (i.e., AP-3, AP-4, GGAs). Dr. Bonifacino applied the knowledge gained from these studies to the elucidation of the causes of various human diseases including the Hermansky-Pudlak syndrome type 2 and autosomal dominant polycystic liver disease. Dr. Bonifacino serves or has served as associate editor of the journals Developmental Cell, Molecular Cell and Molecular Biology of the Cell, and editorial board member of The Journal of Cell Biology, The Journal of Biological Chemistry and Traffic. He is also editor of the book Current Protocols in Cell Biology and Short Protocols in Cell Biology. He has been a member of the Council of the American Society for Cell Biology (ASCB) and chaired various scientific conferences. He has delivered the Alex Novikoff, Leonardo Satz, G. Burroughs Mider, Jesus Adolfo Garcia Sanz and Monod-Diderot lectures, and is an Honorary Professor of Biological Chemistry at the University of Buenos Aires and a Sackler Lecturer at Tel Aviv University, Israel. His lab has trained over 70 post-doctoral fellows and students, most of whom have pursued careers in academic research.

Selected publications (14 of 221)

Bonifacino JS, Suzuki CK and Klausner RD (1990) A peptide sequence confers retention and rapid degradation in the endoplasmic reticulum. *Science* 247, 79-82.

This paper reports that the unusually charged transmembrane domains of T-cell antigen receptor subunits direct degradation of the unassembled proteins by a newly-discovered non-lysosomal, pre-Golgi degradation pathway that is now known as ER-associated degradation (ERAD).

Bonifacino JS, Cosson P and Klausner RD (1990) Colocalized transmembrane determinants for ER degradation and subunit assembly explain the intracellular fate of TCR chains. *Cell* 63, 503-513.

This paper uncovered the fundamental principle that the stability of fully-assembled multi-protein complexes and the degradation of unassembled subunits are dictated by the coincidence of assembly and degradation determinants on the constituent subunits.

Cosson P and Bonifacino JS (1992) Role of transmembrane domain interactions in the assembly of class II MHC molecules. *Science* 258, 659-662.

This study demonstrated that dimerization of transmembrane helices promotes assembly of class II MHC alpha and beta chains. Together with the previous two papers, this study highlighted the role of transmembrane domains in directing the assembly and fate of integral membrane proteins.

Ohno H, Stewart J, Fournier MC, Bosshart H, Rhee I, Miyatake S, Saito T, Gallusser A, Kirchhausen T and Bonifacino JS (1995) Interaction of tyrosine-based sorting signals with clathrin-associated proteins. *Science* 269, 1872-1875.

This highly cited study identified the mu chains of clathrin-associated adaptor protein (AP) complexes as the subunits that recognize tyrosine-based sorting signals involved in targeting to endosomes and lysosomes. This work revolutionized the analysis of signal-adaptor interactions, as it not only provided the first convincing demonstration of this type of interaction, but also established a robust set of assays that enabled further analyses.

Dell'Angelica EC, Ohno H, Ooi CE, Rabinovich E, Roche K and Bonifacino JS (1997) AP-3: an adaptor-like protein complex with ubiquitous expression. *EMBO J*. 16, 917-928.

For a long time, only AP-1 and AP-2 were known to function as clathrin adaptors. This study revealed the existence of a third AP complex, AP-3, which, unlike the other two, was localized to endosomes.

Dell'Angelica EC, Klumperman J, Stoorvogel W and Bonifacino JS (1998) Association of the AP-3 adaptor complex with clathrin. *Science* 280, 431-434

This paper reported that AP-3 is a clathrin adaptor localized to endosomal tubular structures and identified a "clathrin box" motif that was later found in many clathrin-binding proteins.

Dell'Angelica EC, Shotelersuk V, Aguilar RC, Gahl WA and Bonifacino JS (1999) Altered trafficking of lysosomal proteins in Hermansky-Pudlak syndrome due to mutations in the beta3A subunit of the AP-3 adaptor. *Mol. Cell* 3, 11-21.

This study demonstrated that mutations in the beta3A subunit of AP-3 are the cause of the heritable pigmentation and bleeding disorder, Hermansky Pudlak syndrome type 2, the first human disease shown to be the result of a defect in a sorting adaptor. In addition, this study highlighted the role of AP-3 in the biogenesis of lysosome-related organelles such as melanosomes and platelet dense bodies.

Dell'Angelica EC, Puertollano R, Mullins C, Aguilar RC, Vargas JD, Hartnell LM and Bonifacino JS. (2000) GGAs: a family of ADP-ribosylation factor-binding proteins related to adaptors and associated with the Golgi complex. *J. Cell Biol*. 149, 81-93.

This paper reported the discovery of the GGAs, a new family of Arf-regulated adaptor-related proteins localized to the trans-Golgi network and involved in acid hydrolase sorting.

Puertollano R, Randazzo PA, Presley JF, Hartnell LM and Bonifacino JS (2001) The GGAs promote ARF-dependent recruitment of clathrin to the TGN. *Cell* 105, 93-102.

This study showed that the GGAs represent a new type of monomeric clathrin adaptor, distinct from the heterotetrameric AP-1, AP-2 and AP-3 complexes. The GGAs are thus paradigmatic of many other monomeric proteins that are now known to function as clathrin adaptors.

Puertollano R, Aguilar RC, Gorshkova I, Crouch RJ and Bonifacino JS (2001) Sorting of mannose 6-phosphate receptors mediated by the GGAs. *Science* 292, 1712-1716.

This study demonstrated that the GGAs mediate the sorting of mannose 6-phosphate receptors (MPRs) and their cargo acid hydrolases from the trans-Golgi network to endosomes. This role is mediated by recognition of a novel type of di-leucine-based sorting signal in the cytosolic tails of the MPRs by the VHS domain of the GGAs. The structural basis for this interaction was elucidated in subsequent work by Bonifacino and colleagues.

Janvier K, Kato Y, Boehm M, Rose JR, Martina JA, Kim BY, Venkatesan S, and Bonifacino JS (2003) Recognition of dileucine-based sorting signals from HIV-1 Nef and LIMP II by the AP-1 gamma•sigma1 and AP-3 delta•sigma3 hemicomplexes. *J. Cell. Biol*., 163, 1281-1290.

The identity of the AP subunits that recognize another type of di-leucine-based sorting signals (distinct from those recognized by the GGAs) was controversial until this study. Bonifacino and colleagues used various state-of-the-art methodologies to demonstrate that binding of these signals required two subunits from the heterotetrameric AP complexes, thus explaining previous failures to demonstrate binding to single subunits. These observations have now been confirmed and expanded by other groups.

Puertollano R and Bonifacino JS (2004) Interactions of GGA3 with the ubiquitin sorting machinery. *Nat. Cell Biol*., 6, 244-251.

This paper reported that the GGAs function as adaptors for not only proteins having di-leucine-based sorting signals but also ubiquitinated proteins. The structural basis for this interaction was elucidated in subsequent work by Bonifacino and colleagues.

Burgos PV, Mardones GA, Rojas AL, daSilva LL, Prabhu Y, Hurley JH, Bonifacino JS (2010) Sorting of the Alzheimer's disease amyloid precursor protein mediated by the AP-4 complex. *Dev Cell*. 18, 425-436.

This study demonstrated that another adaptor discovered in Bonifacino's lab, AP-4, recognizes a novel type of signal that mediates sorting of the Alzheimer's Disease Amyloid Precursor Protein from the trans-Golgi network to endosomes.

Farías GG, Cuitino L, Guo X, Ren X, Jarnik M, Mattera R and Bonifacino JS (2012) Signal-mediated, AP-1/Clathrin-dependent Sorting of Transmembrane Receptors to the Somatodendritic Domain of Hippocampal Neurons. *Neuron*, 75 810-823.

This study elucidated a role for the AP-1 in the polarized sorting of various transmembrane receptors to the somatodendritic domain of hippocampal neurons.